UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,090	02/03/2004	Margaret H. Baron	HUIP-P02-060	4153

28120 7590 10/26/2009

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
10/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,090	BARON ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-75* is/are pending in the application.

4a) Of the above claim(s) *73 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-72 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *70-75* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/09;8/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The claim listing of 8/5/09 has been entered in full. The status identifiers of the claims have been updated but no changes have been made. Claims 1-69 were previously canceled. Claims 70-75 are pending.

Claim 73 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species (enhanced vascular growth accompanying ocular neovascularization), there being no allowable generic or linking claim.

Election of Species

A further election of species was required in the Office Action mailed 7/1/09.

Applicants' election with traverse of breast cancer as the species of solid tumor in the reply filed on 8/5/09 is acknowledged.

The traversal is on the ground(s) that a search for "breast cancer (Species I) and for hemangioma (Species II) could be carried out simultaneously without imposing a serious burden" because "as both species are forms of solid tumors, a search for solid tumors would reveal art for both breast cancer and hemangioma" (pg 3). Applicants further argue that "the malignancy of the recited solid tumor species, or lack thereof, should not effect [sic] the Examiner's search for, or examination of, either species in the context of the pending claims. As both breast cancer and hemangiomas are associated with increased vascularization or neovascularization regardless of their malignancy status, a search of either of these species would not require a different field of search..."

This is not found persuasive because the art relevant to particular species of cancer does not generally provide any teachings regarding hemangiomas. The art cited previously in the rejection of the claims under 35 U.S.C. 112, 1st paragraph (pg 4-9 of the 10/9/08 Office Action) concerns the hedgehog pathway activity in particular solid tumors, but none of these references discusses the hedgehog pathway signaling in hemangiomas (see Nagase et al, 2008; Yamazaki et al, 2008; Thievessen et al, 2005;

Watkins et al, 2003; Chatel et al, 2007 each cited previously). Thus, it is maintained that the species require a different field of search (e.g., searching different classes/ subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. Thus, it is maintained that there is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics.

The requirement is still deemed proper and is therefore made FINAL.

Claim 74 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 70-72 and 75 are under consideration, as they read upon the elected species.

Information Disclosure Statement

The Information Disclosure Statements of 4/13/09 and 8/5/09 have been considered.

Withdrawn Objections and/or Rejections

The rejection of claims 43, 58, 60 and 69 set forth in the Office Action mailed 10/9/08 is moot in view of Applicants' cancellation of these claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-72 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth previously and maintained at pg 4-11 of the 10/9/08 Office Action for claims 70-72; claim 75 (newly added in the amendments filed on 4/13/09) is herewith added to the rejection.

For clarity, the rejection is first restated in view of Applicants' amendments to the claims filed on 4/13/09, and then Applicants' arguments from the response filed on 4/13/09 are addressed.

Independent claim 70 encompasses a method of inhibiting vascular growth in a subject suffering from excess vascularization or neovascularization, comprising administering an amount of a Sonic hedgehog blocking antibody effective to inhibit abnormally enhanced vascular growth. The elected species of abnormally enhanced vascular growth under consideration is growth is a solid tumor and wherein said solid tumor is breast cancer; claim 71 encompasses, and claim 72 is limited to, said species. Claim 75 limits the method to one wherein the antibody inhibits angiogenesis.

The term "vascular" refers to vessels that circulate biological fluids such as blood or lymph; therefore "vascular growth", "vascularization", and "neovascularization" include vasculogenesis and angiogenesis of blood and lymph vessels. With respect to blood vessels the relevant art teaches, “[i]n vasculogenesis, endothelial cells are differentiated *de novo* from mesodermal precursors, whereas in angiogenesis, new blood vessels are generated from pre-existing ones. Vasculogenesis occurs only during embryonic development and leads to formation of a primary capillary plexus. In angiogenesis, new capillaries form and remodel by budding (sprouting), splitting (intussusception) and fusion (intercalated growth), producing a juvenile vascular system and then a mature one” (pg 2013 of Cohen Jr, 2006. American Journal of Medical Genetics. 140A: 2013-2038; cited previously). However, other teachings in the relevant art suggest that vasculogenesis may also contribute to blood vessel formation in adult mammals; however, the role of this contribution is not well-characterized (see pg 157 of Ribatti et al. 2001. Mechanisms of Development. 100: 157-163; cited previously).

Claim 70 is extremely broad with respect to the encompassed conditions related to vascular growth. Treatment of "vascular growth in a subject suffering from excess vascularization or neovascularization" includes excess vascular growth that occurs in either embryonic vascularization or adult angiogenesis. The specification teaches that conditions of "excess vascularization" or "neovascularization" include "a variety of solid tumors such as breast cancer, hemangiomas in infancy, ocular neovascularization associated with diabetes, bleeding disorders of the female reproductive tract, and certain forms of arthritis" (pg 28, lines 10-13). The specification further teaches, "abnormal vascular growth such as occurs in tumors, rheumatoid arthritis, hemangiomas, angiofibromas, psoriasis and capillary proliferation and diabetes" (pg 2, lines 22-24). The specification also teaches, "a method is further provided for treating abnormal blood vessel formation (hypervascularization) resulting from genetic diseases, chronic degenerative disease, aging, trauma, or infectious agents. Examples include diabetic chronic ulcers, bums, frost bite, ischemic events following stroke and transplantation" (pg 27, lines 26-30). The claims encompass treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. For example, the abnormally enhanced angiogenesis that occurs in ischemia is advantageous for survival of the affected subject rather than harmful. However, the claims lack enablement even with respect to the elected species under consideration (abnormally enhanced vascular growth associated with a solid tumor wherein said tumor is breast cancer). Because the claims are not enabled for this species (for the reasons set forth herein), the enablement of other encompassed species has not been considered.

The specification as originally filed provides minimal guidance to the skilled artisan with respect to practicing the claimed method with any of the envisioned conditions including the elected species (solid tumors wherein said tumor is breast cancer). The specification does not provide any *in vivo* working examples of treatment of a condition of "abnormally enhanced vascular growth" with a "Sonic hedgehog blocking antibody". The specification does not provide any *in vitro* models that correlate with *in vivo* treatment.

Examples 3-6 of the specification provide teachings that are very limited in relation to the claimed inventions. Example 3 teaches that exogenous Sonic hedgehog (Shh) protein added to explant culture can "stimulate hematopoiesis in the epiblast mesoderm" in place of visceral mesoderm (pg 44, lines 6-20). Hematopoiesis was assessed by measuring ε-globin (see description of Figure 9 on pg 8), which the specification teaches as a marker of erythroid cell formation (pg 28, lines 20-21). Example 3 further teaches that Shh or Indian Hedgehog (Ihh) proteins stimulate proliferation adult hematopoietic stem cells isolated from bone marrow and cultured. Example 4 demonstrates that "Shh blocking antibody" reduces ε-globin expression in cultured murine whole embryo (pg 48). Example 5 demonstrates expression of *patched* and *Gli* (genes that encode hedgehog signaling pathway components) that was "substantially exclusive in the yolk sac mesoderm" (pg 48). Example 6 states that, "both *Indian hedgehog* and *BMP-6* are expressed in early visceral endoderm." Based on these results, the specification asserts that hedgehog proteins "have utility in regulating hematopoiesis and vascular growth in the adult animal" (pg 13, lines 24-25). However, these examples in the specification are all related to *in vitro* hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. As taught in the specification, "[i]n contrast to vascular growth, hematopoiesis is normally a continuous process throughout the life of an adult" (pg 2, lines 26-27). There are no examples related to stimulation or inhibition of vascular growth in either an embryo or an adult in either normal or diseased individuals with a solid tumor.

The post-filing date art does support a role for the hedgehog pathway in the growth and angiogenesis of a certain subset of solid tumors. For example, Nagase et al teaches, "Shh signalling has been implicated in the development of several malignancies including basal cell carcinoma of the skin, lung cancer and medulloblastoma … and it is possible the Shh mediates tumor angiogenesis ... Hh signaling may be enhanced, stimulating tumour angiogenesis" (pg 74 of Nagase et al, 2008. Angiogenesis, 11: 71-77; cited previously). Yamazaki et al, 2008 teaches (with respect to pancreatic tumors) "[o]ur results imply that SHH secreted from cancer cells facilitates tumor growth not only by stimulating proliferation of cancer in an autocrine

manner but also by promoting angiogenesis through EPC activation in a paracrine manner" (pg 1137 of Yamazaki et al, 2008. Cancer Sci. 99(6): 1131-1138; cited previously). As such, the instant claims encompass inhibition of abnormally enhanced vascular growth associated with a tumor that occurs by (1) directly, by blocking the Shh stimulating paracrine vascular growth; and/or (2) indirectly, by blocking the Shh stimulating autocrine tumor growth, which in turn prevents additional vascular growth associated with the tumor.

However, the post-filing date art makes it clear that many solid tumors do not include dysfunctions that lead to Shh overexpression. For example, Thievessen et al (2005) teaches, "our data suggest that hedgehog pathway is weakly active in normal adult urothelial cells and of limited importance in TCC [transitional cell carcinoma]" (abstract) and "the hedgehog pathway has been reported to become activated in small cell lung cancer, but not in other histological types of lung cancer" (pg 376 of Thievessen et al, 2005. Journal of Cellular Physiology. 203: 372-377; cited previously). Furthermore, even in small cell lung cancer, Watkins et al observed that only 50% of primary tumors (5 of 10) expressed the Sonic hedgehog protein (see page 314 of Watkins et al, 2003. Nature. 422(6929): 313-7 plus 2 pages of Supplementary material; cited previously; see also Supplementary panel a, the legend for which states "The SCLC case demonstrates [sic] variable co-expression of Shh and Gli1 in tumor cells"). Furthermore, the relevant art teaches that "the published results on primary human colon cancers are also confusing. Some authors, but not others detected increased levels of Hh pathway members during colon cancer progression. Moreover, the expression of Ihh and Gli1 were shown to be decreased during colon cancer progression in recent publications" (see pg 2626 of Chatel et al, 2007. Int J Cancer. 121: 2622-2627; cited previously). Furthermore, U.S. Pre-Grant Application Publication 2004/0110663 (a publication of application 10/652,298; cited on the IDS filed 10/22/07) reports that high levels of *gli-1* expression (as compared with “non-proliferative” cells) are found in some tumors of the prostate, lung, and breast (“8 out of 18 breast cancer samples showed substantially increased gli-1 expression. 7 out of 11 lung cancer samples, 11 of 19 benign prostatic hypertrophy samples (BPH), and 6 out of 15 prostate

cancer samples all showed strong gli1 expression"; ¶ 759 of the '663 publication). The '663 publication further reports that the growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by the Sonic hedgehog blocking antibody 5E1 (Figure 54; ¶ 848). Thus, the art provides evidence that many tumors of different tissues do not include activation of the hedgehog signaling pathway such that Shh is overexpressed. This supports the general concept that different conditions of abnormal vascular growth in adult subjects (e.g., solid tumors from different patients) does not necessarily involve expression of the same angiogenic molecules. This variable expression "not only among different tumour types, but also with the same tumour" has also been observed with vascular endothelial growth factor (VEGF), another molecule associated with angiogenesis (pg 394 of Ferrara et al. 2004. Nature Reviews Drug Discover. 5(3): 391-400; cited previously).

Based on limited working examples showing a role of the Sonic hedgehog protein in *in vitro* hematopoiesis, the instant specification asserts that antagonists of Sonic hedgehog signaling, such as a Sonic hedgehog blocking antibody, can be used to treat abnormally enhanced vascular growth, such as the elected species of solid tumor that is breast cancer. However, the instant specification contains no recognition that aberrant Shh expression is associated only with certain subset of solid tumors. Instead, the instant specification directs the skilled artisan to treat any solid tumor that is breast cancer with a Sonic hedgehog blocking antibody. However, in view of the teachings of the post-filing date art, the skilled artisan would predict that a breast cancer tumor that does not overexpress the Sonic hedgehog protein would fail to be inhibited by administration of a Sonic hedgehog blocking antibody. What is missing from the specification is the critical guidance to first determine that the solid tumor is associated with misregulation of the Sonic hedgehog signaling pathway that results in Shh overexpression. In view of the lack of guidance provided by the specification and the prior art the skilled artisan could not practice the claimed method without undue experimentation.

Applicants' arguments (4/13/09; pg 4-10) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In section A of the 4/13/09 response (pg 4-5), Applicants argue that the claims are not overly broad with respect to the encompassed conditions related to vascular growth. Applicants argue that the claims have been amended such that they refer "with particularity to a certain class of conditions for which inhibition of vascular growth is therapeutically effective" (pg 5); in support Applicants point to paragraph 118 of the specification. Applicants argue that independent "[c]laim 70 does not encompass conditions such as ischemia in which inhibition of vascular growth may be counter-indicated" (pg 5). Applicants further argue that "it would have been clear to the skilled artisan to administer a Shh-blocking antibody only in those cases where inhibition of angiogenesis would be beneficial in treating disease" (pg 4).

These arguments have been fully considered but are not found to be persuasive. The teachings at paragraph 118 regarding conditions related to suffering from excess vascularization or neovascularization are merely exemplary and do not provide a limiting definition of a "subject suffering from excess vascularization or neovascularization". The canceled claims, such as claim 43, were directed to "inhibiting abnormally enhanced vascular growth". The specification does not provide a limiting distinction between "abnormally enhanced vascular growth" and "excess vascularization or neovascularization". Thus, it is maintained that the claims encompass treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. With respect to inoperative embodiments, MPEP 2164.08 "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art". In the instant case, the specification does not provide guidance as to whether or not the claimed treatment method would be effective in treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. For example, the abnormally enhanced angiogenesis that

occurs in ischemia is advantageous for survival of the affected subject rather than harmful. Guidance is not provided in the specification as to whether such treatments are operative or inoperative. The skilled artisan would need to engage in undue experimentation to determine whether or not such treatment(s) are effective.

In section B of the 4/13/09 response (pg 5-7), Applicants argue that the specification provides a working example (Example 4) that provides sufficient guidance to the skilled artisan with respect to practicing the claimed method "by teaching that a Shh blocking antibody could be used for the purposes of inhibiting vascular growth". Applicants argue that the instant specification does not require the presence of an *in vivo* working example. Applicants point to MPEP 2164.02 in support of the argument that enablement does not require presence of a working example, particularly where "there is a well understood connection between inhibition of vascular growth and, for example, therapeutic treatment of tumors" (pg 6). Applicants further argue that "embryonic cultures were described at the filing date as being useful systems for studying the processes of erythropoiesis and vasculogenesis"; Applicants point to Palis et al (1995; Exhibit 1) in support (pg 6).

These arguments have been fully considered but are not found to be persuasive. Example 4 demonstrates that “Shh blocking antibody” reduces ε-globin expression in cultured murine whole embryo (pg 48). As elaborated below, it is maintained that ε-globin expression is a marker for hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. Thus, it is maintained that there are no examples in the specification related to stimulation or inhibition of vascular growth in either an embryo or an adult in either normal or diseased individuals with a solid tumor. Furthermore, the connection between inhibition of vascular growth and therapeutic treatment of tumors is not disputed; however, it is disputed that vascular growth of tumors necessarily involves Shh activity such that blocking such activity would inhibit the vascular growth. The relevant art provides evidence that tumor-associated angiogenesis is a paracrine effect dependent on secretion of Shh from the tumor (see the teachings of Yamazaki et al, 2008 cited above). There is no evidence in the relevant art that Shh plays a role in tumor

angiogenesis independent of tumor expression of Shh. Furthermore, it is not disputed that Palis et al teaches an "explant system" that "allows the study of the molecules involved in the initial development of mammalian yolk sac blood cells and vascular networks". However, Palis et al does not teach such a system as a model for excess neovascularization in later development (e.g., adult tissues). As noted above in the rejection, the relevant art teaches a distinction between vasculogenesis in embryonic development and angiogenesis in later tissues (see citation above from Cohen et al, 2006).

In section C of the 4/13/09 response (pg 7-8), Applicants argue that Examples 3-6 of the specification support the scope of the claimed invention. Applicants dispute the contention that Examples 3-6 provide teachings that are very limited in relation to the claimed invention. Applicants argue that that ε-globin was used as a marker in Example 3-6, and the specification teaches that ε-globin is not just a marker of hematopoiesis, but also of vascular growth. Applicants point to paragraphs [0015], [0089] and [0090] in support. Applicants argue that hemoglobin is commonly used marker for both angiogenesis and vasculogenesis in the relevant art. Applicants point to the references of Robertson et al, 1991; Hu et al, 1993; Teunis et al, 2002; Yoshida et al, 2003; and Fang et al, 2007 (Exhibits 2-6).

These arguments have been fully considered but are not found to be persuasive. It is not disputed that each of the cited references teaches elevation of hemoglobin expression in particular tissues as a marker of angiogenesis. However, in each of these references, the measured angiogenesis occurred in adult tissues and the measured hemoglobin was adult hemoglobin. As noted above in the rejection, the relevant art teaches a distinction between vasculogenesis in embryonic development and angiogenesis in later tissues (see citation above from Cohen et al, 2006). Furthermore, the hemoglobin subunit ε-globin is expressed only in the embryonic yolk sac and is replaced by other subunits in fetal and adult tissues. Furthermore, the relevant art teaches a distinction between markers of primitive erythroblasts and vascular endothelial cells. Dyer et al (2001. Development. 128: 1717-1730; reference BC on the 2/3/04 IDS) teaches a distinction between primitive hematopoietic (ε- and β-*globin*,

Gata1 and *Cd34*) and endothelial (*Vezf1*, *Pecam* and *Flk1*) markers. Thus, it is not persuasive that ε-globin is considered a marker of vasculogenesis in embryonic development. The while the specification indicates that the Examples in the specification relate to both hematopoiesis and vasculogenesis, this is held to be speculative as there is insufficient evidence that ε-globin is considered a marker of embryonic vasculogenesis in the relevant art.

In section D of the 4/13/09 response (pg 8-10), Applicants argue that the claims are enabled for the treatment of solid tumors using a Shh blocking antibody. Applicants state that they "maintain their argument, as previously put forth in the June 25, 2008 Response [sic], that the claimed invention is not based on necessarily modulating hedgehog signaling in tumor cells, but rather on inhibiting enhanced vascular growth, such as the vascular growth accompanying a solid tumor" (pg 8). Applicants further argue that it is well understood in the art that angiogenesis is crucial for growth of most malignant solid tumors, even if "Shh overexpression may not be observed in all tumors". Applicants argue that the specification provides teachings such that the skilled artisan could administer Shh blocking antibody to inhibit block Shh signaling and thus inhibit angiogenesis in "developing solid tumors - regardless of whether the tumor itself is characterized by misregulation in hedgehog signaling" (pg 8). Applicants further argue that "although the references pointed to by the Examiner state that many solid tumors are not themselves characterized by Shh overexpression, none of these references address the subject matter presently claimed" because they "do not examine angiogenesis associated with these tumors" (pg 8).

These arguments have been fully considered but are not found to be persuasive. It is maintained that in view of the relevant teachings of the post-filing date art (cited in the rejection above), administration of a Sonic hedgehog blocking antibody would not result in treatment of a solid tumor unless the tumor exhibits overexpression of the Sonic hedgehog protein. It is acknowledged that determination of the specific mechanism of dysregulation leading to such overexpression is not needed, but determination of such overexpression is necessary to identify those tumors that can be successfully treated with the blocking antibody. It is not disputed that inhibition of

angiogenesis is a widely acknowledged strategy in the art for tumor treatment. However, Applicants have provided no evidence that a hedgehog antagonist such as a blocking antibody can inhibit the vascular growth associated of the many solid tumors in which the Sonic hedgehog antibody is not overexpressed. The relevant art provides evidence that tumor-associated angiogenesis is a paracrine effect dependent on secretion of Shh from the tumor (see the teachings of Yamazaki et al, 2008 cited above). There is no evidence in the relevant art that Shh plays a role in tumor angiogenesis independent of tumor expression of Shh.

Applicants further argue that the fact that the 5E1 antibody did not inhibit the growth of the solid tumor does not address the question of whether the Sonic hedgehog antibody inhibited vascular growth associated with the tumor. Applicants further argue that the SW480 cell line used in making xenograft "may generate an idiosyncratic class of tumors that, in contrast to most solid tumors, are not largely driven by angiogenesis" (pg 10). In support, Applicants point to evidence that SW480 express relatively low levels of the angiogenic-inducing factor VEGF" (Ellis et al, 2000; Exhibit 7) and "a form of p53, a known inhibitor of angiogenesis, that has retained some of its normal activity" (Rochette et al, 2005; Exhibit 8).

These arguments have been fully considered but are not found to be persuasive. The instant specification sets forth the accepted model of solid tumor growth in paragraph 60: "[v]ascular growth occurs … in a variety of diseases including cancer, where a tumor releases factors that stimulate sprouting of blood vessels in normal tissue where the new blood vessels are directed into the tumor tissue". Applicants provide no evidence that the tumors created from the SW480 cell line can grow without said corresponding vascular growth. Ellis et al merely state that SW480 expresses "relatively low" VEGF without addressing vascular growth. Likewise, Rochette et al does not address vascular growth of tumors formed by the SW480 cell line. Applicants' argument that the basis of the antibody's failure to inhibit SW480 growth is a lack of a requirement for angiogenesis is a hypothetical argument unsupported by evidence. Thus, it is maintained that the results described in the '663 publication (that growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by

the Sonic hedgehog blocking antibody 5E1 (Figure 54; ¶ 848)) is a further example of solid tumors that do not include dysfunctions that lead to Shh overexpression.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647